# Impact of BRCA1/2 testing and disclosure of a positive test result on women affected and unaffected with breast or ovarian cancer

van Roosmalen, MS; Stalmeier, PFM; Verhoef, LCG; Hoekstra-Weebers, JEHM; Oosterwijk, JC; Hoogerbrugge, N; Moog, U; van Daal, WAJ

*Published in:*
American Journal of Medical Genetics. Part A

*DOI:*
10.1002/ajmg.a.20374

American Journal of Medical Genetics 124A:346–355 (2004)

# Impact of *BRCA1/2* Testing and Disclosure of a Positive Test Result on Women Affected and Unaffected With Breast or Ovarian Cancer

**Mariëlle S. van Roosmalen,[1]* P.F.M. Stalmeier,[1,2] L.C.G. Verhoef,[1] J.E.H.M. Hoekstra-Weebers,[3] J.C. Oosterwijk,[4] N. Hoogerbrugge,[5] U. Moog,[6] and W.A.J. van Daal[1]**

[1]*Department of Radiotherapy (341), University Medical Center Nijmegen, Nijmegen, The Netherlands*
[2]*Department of Medical Technology Assessment, University of Nijmegen, Nijmegen, The Netherlands*
[3]*Department of Medical Psychology, University Hospital Groningen, Groningen, The Netherlands*
[4]*Department of Clinical Genetics, University Hospital Groningen, Groningen, The Netherlands*
[5]*Department of Human Genetics and Hereditary Cancer Clinic, University Medical Center Nijmegen, Nijmegen, The Netherlands*
[6]*Department of Clinical Genetics, University Hospital Maastricht, Maastricht, The Netherlands*

**To evaluate the impact of *BRCA1/2* testing and disclosure of a positive test result on women affected and unaffected with cancer. Longitudinal cohort study including women affected and unaffected with breast or ovarian cancer testing for a *BRCA1/2* mutation. Data on well-being (anxiety, depression, cancer related distress, general health), treatment choice, and decision making about cancer prevention were collected at baseline (1 week after blood sampling; affected n = 192, unaffected n = 176) and at follow-up (2 weeks after disclosure of a positive test result; affected n = 23, unaffected n = 66). Women affected and unaffected with breast or ovarian cancer were compared using univariate statistics. Change over time was examined using repeated measures analysis of variance. With respect to well-being, affected women scored worse at baseline. At follow-up, both affected and unaffected women experienced a decline in well-being, which tended to be stronger in affected women. Women diagnosed with cancer less than 1 year previously tended to report a worse well-being than those diagnosed longer ago. With respect to treatment choice, more affected women intended to obtain prophylactic surgery and valued it higher at both time points. With respect to decision making, affected women had a lower preference for participation in decision making at baseline; no differences were found at follow-up. At follow-up, both affected and unaffected women showed an increase in strength of treatment preference and a decrease in decision uncertainty. Disclosure of a positive test result had a negative impact on well-being. Affected women, especially those who have been recently diagnosed with cancer, experienced the worst well-being and could benefit from psychosocial support.**


**KEY WORDS: genetic testing; *BRCA1/2* mutation; well-being; decision making**

## INTRODUCTION

The identification of the *BRCA1* and *BRCA2* genes has created the possibility to test for inherited susceptibility of breast and ovarian cancer [Miki et al., 1994; Wooster et al., 1995]. Diagnostic genetic testing in a family usually begins in a woman affected with cancer (index case). Once a mutation is detected, predictive testing can be performed in other family members. Affected mutation carriers have a high risk of developing a second cancer [Ford et al., 1998]. Unaffected mutation carriers have a high cumulative lifetime risk for breast (56 to 85%) and ovarian cancer (16 to 63%) [Easton et al., 1995; Struewing et al., 1997; Whittemore et al., 1997; Ford et al., 1998]. In the Netherlands, mutation carriers currently face the difficult choice between prophylactic surgery and screening of breasts and/or ovaries.

Grant sponsor: Dutch Cancer Society, Amsterdam, the Netherlands; Grant number: NUKC 98-1585.

*Correspondence to: Mariëlle S. van Roosmalen, Department of Radiotherapy (341), University Medical Center Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
E-mail: m.vanroosmalen@rther.umcn.nl

Received 14 November 2002; Accepted 1 May 2003
DOI 10.1002/ajmg.a.20374

Because genetic testing and disclosure of a positive test result may have far reaching consequences for both affected and unaffected women, it is important to monitor the impact on well-being and decision making about cancer prevention. A priori, one might assume that genetic testing and disclosure of a positive test result may cause distress. However, previous studies evaluating the impact of genetic testing and disclosure of a positive test result, showed low levels of general and cancer related distress [Lerman et al., 1996; Croyle et al., 1997; Lodder et al., 1999, 2001; Coyne et al., 2000; Wood et al., 2000; Schwartz et al., 2002]. Some of these studies evaluated changes in pre- and post-test distress and found that mutation carriers showed no significant increase in distress after learning their carrier status [Lerman et al., 1996; Croyle et al., 1997; Wood et al., 2000; Lodder et al., 2001; Schwartz et al., 2002].

Until now, no study specifically concentrated on the differential impact of genetic testing on women affected with cancer versus those unaffected. One study, including women anticipating and receiving genetic testing, reported that affected and unaffected women had similar levels of distress [Coyne et al., 2000]. Another study evaluated the impact of a positive test result and found that mutation carriers with a history of cancer or cancer-related surgery were less distressed than those without such a history [Croyle et al., 1997]. A recent study, including both affected index cases and their unaffected relatives, looked at the impact of the test result within those groups and not between those groups [Schwartz et al., 2002].

The purpose of the present study was to evaluate the impact of *BRCA1/2* testing and disclosure of a positive test result on women affected and unaffected with breast or ovarian cancer. We looked at a broad spectrum of outcomes considering well-being and decision making. Because little is known about the impact of genetic testing and disclosure of a positive test result on affected versus unaffected women, knowledge of the levels of distress and the need for help to cope and make decisions may help to improve educational and counseling programs.

This report is subsumed within a larger randomized controlled trail on shared decision making. It was not the primarily objective of that study to focus on the differences between women affected and unaffected with cancer. However, because we hypothesized that affected women are different from unaffected women with respect to well-being and decision making, we conducted an interim analysis to compare affected and unaffected women. When resources for supportive services are scarce, it is important to distinguish those who might benefit the most from additional support.

## METHODS

### Study Population

Women affected and unaffected with breast or ovarian cancer, who provided a blood sample for *BRCA1/2* testing at the Family Cancer Clinics of the University Hospitals of Nijmegen (accrual started March 1999), Groningen (accrual started June 1999), and Maastricht (accrual started January 2000), were eligible for participation. The Eastern part of the Netherlands is covered by these three clinics. Study entry closed in November 2001. Women were excluded from the study if they were unable to give informed consent, had insufficient proficiency of the Dutch language, had distant metastases, had undergone bilateral mastectomy and oophorectomy. Women recently treated for cancer (less than 1 months ago) were also excluded because we assumed that these women were still recovering and were more engaged with the outcomes of the curative treatment than with decision making about cancer prevention.

### Study Procedure

Data were collected during a longitudinal randomized trial on shared decision making including two decision aids. This study was approved by the local research ethics committees. This paper only reports the baseline (1 week after blood sampling) and a follow-up assessment (2 weeks after disclosure of a positive test result) for affected and unaffected women. During this time period, women had received the first decision aid either before or after disclosure of a positive test result; this decision aid consisted of a brochure and video providing detailed information on prophylactic surgery and screening and the consequences. This informative decision aid had positive effects on information related outcomes only, and none, whatsoever, on well-being and decision making. Though, it did lead to more considerations towards prophylactic surgery and higher valuations for prophylactic surgery and lower valuations for screening. Furthermore, because timing of the decision aid had no effect, all women at follow-up were equal on the outcome measures [Van Roosmalen et al., 2002b]. The second decision aid, consisting of value assessment and individualized treatment information, will be evaluated only in *BRCA1/2* mutation carriers. The follow-up time point reported here, will be the baseline assessment for this second intervention.

Clinical geneticists or genetic counselors briefly introduced the study when a blood sample for genetic testing was obtained. A research assistant subsequently contacted these women by phone to confirm eligibility and to discuss the study. Women who gave verbal consent were enrolled and were mailed an informative letter describing the study, a consent form, and the baseline questionnaire. Two weeks after a positive test result, women received a follow-up questionnaire by mail.

### Standard Genetic Counseling

Before a blood sample for genetic testing is taken, usually two counseling sessions with a genetic counselor or clinical geneticist take place including the following: clarification of the patient's increased risk status, explanation of genetic cancer susceptibility, information on the pros and cons of genetic testing, the possible outcomes of testing, and limited data regarding cancer screening and prophylactic surgery. When a mutation is found, more detailed information is provided on the

possible treatment options and women are offered additional consultations with specialist physicians (medical oncologist, gynecologist, and surgeon). These appointments usually take place a view weeks after testing positive for a *BRCA1/2* mutation, this is after the follow-up assessment reported here. A social worker or a psychologist is generally present when a positive test result is disclosed to unaffected women.

## MEASURES

### Baseline Variables

***Sociodemographics and medical history.*** Data were obtained on sociodemographics (age, marital status, education level, employment status, presence of children, wanting (more) children, being religiously affiliated) and medical history (personal and family history of breast/ovarian cancer, time since last cancer diagnosis, being an index case, having first degree relatives with breast/ovarian cancer, having first degree relatives who died of breast/ovarian cancer).

### Outcome Variables

***Well-being***

*Anxiety.* Anxiety was measured using the 20 items of the State Anxiety scale of the Spielberger State-Trait Anxiety Inventory (STAI) [Spielberger et al., 1983]. Sum scores on this measure range from 20 to 80, with higher scores representing higher levels of anxiety.

*Depression.* Depression was measured using the 20 items of the Center for Epidemiologic Studies Depression Scale (CES-D) [Radloff, 1977]. Sum scores on this measure range from 0 to 60, with higher scores reflecting more depressive symptoms.

*Cancer related distress.* Cancer related distress was measured with the Impact of Event Scale (IES) [Horowitz et al., 1979]. The two subscales "intrusion" (seven items) and "avoidance" (eight items) measure becoming overwhelmed by thoughts and feelings about cancer in the family and a tendency to avoid these thoughts and feelings respectively. A four-point response scale ranging from "not at all" to "often" was employed and coded 0, 1, 3, and 5. Sum scores on this measure range from 0 to 75, with higher scores indicating more distress.

Adequate reliability rates for the above measures on psychological well-being have been reported previously in comparable samples [Lerman et al., 1996; Croyle et al., 1997]. Consistent with past studies, the Cronbach's coefficients alpha in our sample for the STAI-state, CESD and IES were 0.95, 0.91, and 0.87, respectively.

*General health.* Women were asked to rate their general health state during the last week on a 11-point rating scale (0, very bad; 10, excellent).

***Treatment choice.*** At baseline, women were asked their intended treatment choice if found to be mutation carrier. For the decision related to the breasts and ovaries, the choice was between "prophylactic surgery," "screening," and "undecided." At follow-up, mutation carriers were asked their intended treatment choice using the same alternatives. To test differences in treatment choice, treatment choice was dichotomized into prophylactic surgery versus another treatment choice (i.e., "screening" and "undecided"). Furthermore, women were asked to value the treatment options "prophylactic mastectomy," "breast cancer screening," "prophylactic oophorectomy," and "ovarian cancer screening" on a 10-point rating scale (1, very bad; 10, excellent).

***Decision making.*** The following three outcomes were asked separately for the decision related to the breasts and ovaries. An overall score was created by adding the scores on the items for the decision related to the breast and ovaries and by dividing this sum score by the total number of items.

*Strength of treatment preference.* Strength of treatment preference was assessed on a four-point Likert scale (1, weak preference; 4, very strong preference). Those who had chosen "undecided" as treatment choice were assigned a value of zero (no preference).

*Decision uncertainty.* Decision uncertainty was measured using three items from the uncertainty subscale of the Decisional Conflict Scale by O'Connor [O'Connor, 1995] and adapted for this situation. Our items were: "I doubt what to choose," "This decision is hard for me to make," and "I am not sure what to choose." A five-point scale (1, very much disagree; 5, very much agree) was used. The Cronbach's coefficient alpha was 0.89.

*Preference for decision making.* Preference for decision making was measured using the following two decision making items from the Problem-Solving Decision-Making Scale (PSDM) from Deber et al. [1996]. The items were: "Given the risks and benefits of the possible treatment options, who should decide how acceptable those risks and benefits are for you," and "Given the risks and benefits of the possible treatment options, who should decide which treatment option should be selected." A five-point scale (1, doctor alone; 3, doctor and I equally; 5, I alone) was used. The Cronbach's coefficient alpha was 0.87.

***Statistics.*** In multi-item scales with missing data, we calculated scale values if at least half of the items were filled out. We used the Statistical Package for the Social Sciences (SPSS 10.0.5) to analyze the data.

Descriptive statistics were generated to describe the total sample and the subsample of mutation carriers in terms of sociodemographics and medical history. Differences between affected and unaffected women on the baseline variables and on the outcome variables (at baseline and at follow-up) were explored using univariate statistics ($t$-tests for independent samples and $\chi^2$-tests). Repeated measures analyses of variance were performed to examine change over time (impact of a positive test result) on well-being and decision making, with cancer history (affected versus unaffected) as between-groups factor. Levels of $P \leq 0.05$ (two-tailed) were regarded as statistically significant.

Because a previous study [Wood et al., 2000] found that women recently diagnosed with cancer experienced the greatest distress, additional analyses were done within the group of affected women. Differences between women diagnosed with cancer $\leq$1 year previously and those diagnosed $>$1 year in well-being (at baseline and at

follow-up) were explored using univariate statistics (*t*-tests for independent samples). We also conducted repeated measures analysis of variance to examine change over time (impact of a positive test result) on well-being, with time since diagnosis (≤1 year versus >1 year) as between-groups factor.

## RESULTS

### Participants

During the study period, 453 eligible women were asked to participate in a longitudinal randomized trial on shared decision making. The initial participation rate was 86% (n = 390). Of the 390 women, 22 (6%) dropped out between baseline and disclosure of the test result; 11 affected and 11 unaffected. Of these 22 women, 5 withdrew for emotional reasons related to the informative decision aid (4 affected and 1 unaffected). All baseline analyses are on the remaining 368 women; 192 were affected and 176 were unaffected. Of the 192 affected women, 23 received a positive test result (20 *BRCA1*, 3 *BRCA2*). Of the 176 unaffected, 68 received a positive test result (47 *BRCA1*, 21 *BRCA2*). Within the subgroup of mutation carriers, all 23 affected women were followed up, but 2 of the 68 unaffected women (3%; 1 *BRCA1* and 1 *BRCA2*) withdrew because of high distress caused by the test result.

### Baseline Variables

Table I presents the sociodemographics and medical history of the affected and unaffected women both within the total sample and the subsample of mutation carriers. Within the total sample, several differences between affected and unaffected women were found: (1) affected women were older ($t = 7.62$; $P < 0.001$), (2) had children more often ($\chi^2 = 13.90$; $P < 0.001$), (3) wanted (more) children less often ($\chi^2 = 37.99$; $P < 0.001$), (4) were religiously affiliated more often ($\chi^2 = 8.01$; $P < 0.01$), (5) had a family history of breast cancer only more often ($\chi^2 = 71.44$; $P < 0.001$), (6) were an index case more often ($\chi^2 = 264.91$; $P < 0.001$), and (7) had first degree relatives who had died of cancer less often ($\chi^2 = 8.59$; $P < 0.01$). Within the subsample of mutation carriers, similar differences were found in 1, 3, 5, and 6, but not in 2, 4, and 7.

### Outcome Variables

***Well-being.*** Table II presents the mean scores on well-being and the results of the independent *t*-tests for affected versus unaffected women in the total sample at baseline. Affected women had higher scores on depression and cancer related distress, and a lower score on general health.

The fifth column of Table III presents the mean scores on well-being for affected and unaffected women in the subsample of mutation carriers at follow-up; the results of the independent *t*-tests are not presented. No differences were found for any of the well-being outcomes, although affected women tended to score higher on anxiety ($t = 1.82$, $P = 0.07$).

The last three columns of Table III present the results of the repeated measures analysis of variance; no main

TABLE I. Baseline Variables for the Total Sample and the Subsample of Mutation Carriers Per Group (Affected and Unaffected)

| | Total | | Mutation carriers | |
|---|---|---|---|---|
| | Affected (n = 192) | Unaffected (n = 176) | Affected (n = 23) | Unaffected (n = 66) |
| Sociodemographics | | | | |
| Age: mean (SD) | 47.4 (9.8)* | 39.4 (10.4)* | 44.9 (6.2)* | 37.6 (10.3)* |
| Currently married/partner (%) | 83 | 86 | 83 | 86 |
| College or higher (%) | 25 | 24 | 35 | 24 |
| Employed (%) | 62 | 68 | 70 | 70 |
| Have children (%) | 89* | 74* | 83 | 68 |
| Want (more) children (%) | 4* | 28* | 0* | 33* |
| Religiously affiliated (%) | 71* | 57* | 63 | 62 |
| Medical history | | | | |
| Personal medical history of bc/oc | | | | |
| No cancer (%) | — | 100 | — | 100 |
| Breast cancer only (%) | 90 | — | 100 | — |
| Ovarian cancer only (%) | 8 | — | 0 | — |
| Breast and ovarian cancer (%) | 2 | — | 0 | — |
| Family medical history of bc/oc | | | | |
| Breast cancer only (%) | 74* | 27* | 59* | 12* |
| Ovarian cancer only (%) | 2* | 5* | 0* | 4* |
| Breast and ovarian cancer (%) | 24* | 68* | 41* | 84* |
| Time since last cancer diagnosis: mean (SD) | 4.7 (5.9) | — | 5.2 (5.9) | — |
| Index case | 95* | 11* | 78* | 4* |
| Having first degree relatives with bc/oc (%) | 57 | 66 | 70 | 65 |
| Having first degree relatives who died of bc/oc (%) | 24* | 38* | 35 | 33 |

bc, breast cancer; oc, ovarian cancer.
*Significant difference ($P \leq 0.05$) between affected and unaffected women (independent *t*-test, $\chi^2$-test).

TABLE II. Mean Scores (SD) on the Outcome Variables and Independent *t*-Tests for Affected Versus Unaffected Women in the Total Sample at Baseline

| | Affected | | Unaffected | | | |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | t | *P* |
| Well-being | | | | | | |
| Anxiety (STAI-state) | 187 | 40.6 (11.0) | 176 | 38.8 (11.2) | 1.50 | 0.14 |
| Depression (CESD) | 191 | 10.0 (8.6) | 176 | 7.6 (8.0) | 2.81 | 0.01 |
| Cancer related distress (IES) | 187 | 20.7 (15.0) | 176 | 17.4 (13.0) | 2.20 | 0.03 |
| General health | 192 | 7.3 (1.6) | 174 | 7.6 (1.5) | −2.10 | 0.04 |
| Decision making | | | | | | |
| Valuation of PM | 167 | 5.6 (2.4) | 173 | 4.4 (2.6) | 4.48 | <0.001 |
| Valuation of BS | 170 | 7.1 (2.4) | 174 | 7.7 (2.3) | −2.20 | 0.03 |
| Valuation of PO | 168 | 7.1 (2.2) | 170 | 6.5 (2.7) | 2.14 | 0.03 |
| Valuation of OS | 168 | 6.2 (2.7) | 169 | 6.1 (3.0) | 0.17 | 0.86 |
| Strength of treatment preference | 148 | 2.5 (1.1) | 165 | 2.7 (1.1) | −1.54 | 0.13 |
| Decision uncertainty | 167 | 2.9 (1.1) | 173 | 2.6 (1.1) | 1.85 | 0.07 |
| Preference for decision making | 158 | 3.5 (0.6) | 172 | 3.8 (0.6) | −3.57 | <0.01 |

PM, prophylactic mastectomy; BS, breast cancer screening; PO, prophylactic oophorectomy; OS, ovarian cancer screening.

TABLE III. Mean Scores (SD) on the Outcome Variables (at Baseline and at Follow-Up) and Repeated Measures Analysis of Variance for Affected Versus Unaffected Women in the Subsample of Mutation Carriers

| | | | Mean (SD) | | Test of overall trend | | |
|---|---|---|---|---|---|---|---|
| | | N | Baseline | Follow-up | Effect | F | *P* |
| Well-being | | | | | | | |
| Anxiety (STAI-state) | Affected | 23 | 40.4 (11.5) | 44.7 (11.1) | Ca | 1.98 | 0.16 |
| | Unaffected | 64 | 38.5 (10.9) | 39.3 (12.7) | Time | 5.24 | 0.03 |
| | | | | | Interact | 2.48 | 0.12 |
| Depression (CESD) | Affected | 23 | 8.7 (8.3) | 12.7 (8.7) | Ca | 0.87 | 0.35 |
| | Unaffected | 63 | 7.9 (7.8) | 9.7 (10.7) | Time | 10.22 | <0.01 |
| | | | | | Interact | 1.59 | 0.21 |
| Cancer related distress (IES) | Affected | 22 | 17.6 (13.1) | 25.2 (12.3) | Ca | 0.50 | 0.48 |
| | Unaffected | 64 | 17.9 (13.3) | 20.5 (15.4) | Time | 12.55 | <0.01 |
| | | | | | Interact | 3.00 | 0.09 |
| General health | Affected | 22 | 7.8 (1.3) | 7.1 (1.5) | Ca | 0.77 | 0.38 |
| | Unaffected | 60 | 8.0 (1.6) | 7.6 (1.9) | Time | 6.77 | 0.01 |
| | | | | | Interact | 0.70 | 0.41 |
| Decision making | | | | | | | |
| Valuation of PM | Affected | 21 | 5.3 (2.4) | 6.7 (2.3)* | Ca | 6.13 | 0.02 |
| | Unaffected | 64 | 4.3 (2.7) | 4.8 (2.6)* | Time | 13.18 | <0.001 |
| | | | | | Interact | 2.72 | 0.10 |
| Valuation of BS | Affected | 21 | 7.0 (1.8) | 6.0 (2.2) | Ca | 5.02 | 0.03 |
| | Unaffected | 64 | 8.0 (2.1) | 7.0 (2.3) | Time | 15.82 | <0.001 |
| | | | | | Interact | 0.00 | 0.98 |
| Valuation of PO | Affected | 20 | 6.8 (2.3) | 7.6 (2.3) | Ca | 1.86 | 0.18 |
| | Unaffected | 60 | 6.0 (2.9) | 6.7 (2.7) | Time | 7.58 | 0.01 |
| | | | | | Interact | 0.10 | 0.75 |
| Valuation of OS | Affected | 20 | 5.7 (2.6) | 4.7 (2.5) | Ca | 2.13 | 0.15 |
| | Unaffected | 60 | 6.7 (2.9) | 5.7 (2.9) | Time | 12.05 | <0.01 |
| | | | | | Interact | 0.00 | 0.98 |
| Decision making | | | | | | | |
| Strength of treatment pref. | Affected | 19 | 24 (1.1) | 3.3 (0.6) | Ca | 0.00 | 0.98 |
| | Unaffected | 58 | 2.8 (1.1) | 2.9 (0.9) | Time | 9.80 | <0.01 |
| | | | | | Interact | 7.89 | 0.01 |
| Decision uncertainty | Affected | 21 | 2.8 (1.1) | 2.2 (1.0) | Ca | 0.42 | 0.52 |
| | Unaffected | 61 | 2.6 (1.1) | 2.2 (1.0) | Time | 12.38 | <0.01 |
| | | | | | Interact | 0.37 | 0.55 |
| Preference for DM | Affected | 20 | 3.5 (0.6) | 3.7 (0.8) | Ca | 1.12 | 0.29 |
| | Unaffected | 61 | 3.7 (0.6) | 3.8 (0.7) | Time | 1.51 | 0.22 |
| | | | | | Interact | 0.49 | 0.49 |

Ca, cancer history; Interact, interaction between cancer history and time; PM, prophylactic mastectomy; BS, breast cancer screening; PO, prophylactic oophorectomy; OS, ovarian cancer screening; DM, decision making.
*Significant difference ($P \leq 0.05$) between affected and unaffected women at follow-up (independent *t*-test).

effect of cancer history (affected versus unaffected), a main effect of time (impact of a positive test result), and no interaction of cancer history and time was found for all outcomes. So both affected and unaffected women reported an increase in anxiety, depression, and cancer related distress, and a decrease in general health over time. Although the interactions of cancer history and time were not significant, the positive test result tended to have a greater impact on anxiety and cancer related distress in affected women.

***Well-being and time since diagnosis.*** Table IV presents the mean scores on well-being and the results of the independent *t*-tests for affected women diagnosed with cancer $\leq$1 year previously versus those diagnosed $>$1 year at baseline. Affected women diagnosed $\leq$1 year scored higher on anxiety, depression, and cancer related distress. In fact, affected women diagnosed $>$1 year and unaffected women had similar baseline scores, as can be seen by comparing Table II column 5 with Table IV column 5.

The fifth column of Table V present the mean scores on well-being for affected women diagnosed $\leq$1 year and $>$1 year in the subsample of mutation carriers at follow-up; the results of the independent *t*-tests are not presented. Affected women diagnosed $\leq$1 year scored higher on anxiety ($t = 2.06$, $P = 0.05$) and cancer related distress ($t = 2.11, P = 0.05$). Again, affected women diagnosed $>$1 year and unaffected women had similar follow-up scores, as can be seen by comparing Table III column 5 with Table V column 5.

The last three columns of Table V present the results of the repeated measures analysis of variance; no interaction of time since diagnosis ($\leq$1 year versus $>$1 year) and time (impact of a positive test result) was found for any of the outcomes.

***Treatment choice.*** At baseline, within the total sample, more affected than unaffected women intended to obtain prophylactic mastectomy ($\chi^2 = 8.86$; $P < 0.01$); no difference was found for the treatment choice related to the ovaries ($\chi^2 = 0.42$; $P = 0.52$). At follow-up, within the subsample of mutation carriers, more affected than unaffected women intended to obtain prophylactic oophorectomy ($\chi^2 = 3.96$; $P = 0.05$); no difference was found for the treatment choice related to the breasts ($\chi^2 = 1.58$; $P = 0.21$).

Table VI presents the intended treatment choice related to the breasts and ovaries for affected and unaffected mutation carriers, at baseline and at follow-up. At follow-up, all affected women had made a treatment choice, while some unaffected women were still undecided. From baseline to follow-up, most mutation carriers did not change their intended treatment choice.

***Decision making.*** Table II presents the mean scores on the decision making outcomes and the results of the independent *t*-tests for affected versus unaffected women in the total sample at baseline. Affected women had higher valuations for prophylactic mastectomy and oophorectomy, and a lower valuation for breast cancer screening. Furthermore, affected women had a lower preference for decision making, and tended to report a higher decision uncertainty.

The fifth column of Table III presents the mean scores on the decision making outcomes for affected and unaffected women in the subsample of mutation carriers at follow-up; the results of the independent *t*-tests are not presented. Affected women had a higher valuation for prophylactic mastectomy ($t = 2.98$; $P \leq 0.01$). No differences were found for the other decision making outcomes.

The last three columns of Table III present the results of the repeated measures analysis of variance. A main effect of cancer history (affected versus unaffected) was found for the valuation of prophylactic mastectomy and breast cancer screening; affected women had a higher valuation for prophylactic mastectomy and a lower valuation for breast cancer screening. Also, a main effect of time (impact of a positive test result) was found for all decision making outcomes except the preference for decision making; both affected and unaffected women reported a higher valuation for prophylactic surgery, a lower valuation for screening, an increase in strength of treatment preference, and a decrease in decision uncertainty over time. Finally, an interactive effect of cancer history and time was found for strength of treatment preference; strength of treatment preference increased stronger over time for affected women.

## DISCUSSION

### Summary of Results

This study is the first to show that general (STAI-state, CES-D) and cancer related distress (IES) increase when assessed 2 weeks after disclosure of a positive *BRCA1* or *BRCA2* test result in a relatively large sample of mutation carriers. The sample size enabled us to

TABLE IV. Mean Scores (SD) on Well-Being and Independent *t*-Tests for Affected Women Diagnosed $\leq$1 Year Versus $>$1 Year at Baseline

| | Diagnosed $\leq$1 year | | Diagnosed $>$1 year | | | |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | t | *P* |
| Well-being at baseline | | | | | | |
| Anxiety (STAI-state) | 91 | 42.4 (10.9) | 93 | 38.9 (11.0) | 2.14 | 0.03 |
| Depression (CESD) | 92 | 11.4 (8.3) | 96 | 8.7 (8.6) | 2.20 | 0.03 |
| Cancer related distress (IES) | 91 | 23.2 (15.2) | 93 | 18.8 (14.5) | 1.99 | 0.05 |
| General health | 92 | 7.1 (1.6) | 97 | 7.4 (1.6) | −1.18 | 0.24 |

TABLE V. Mean Scores (SD) on Well-Being (at Baseline and at Follow-Up) and Repeated Measures Analysis of Variance for Affected Women Diagnosed ≤1 Year Versus >1 Year in the Subsample of Mutation Carriers

| | | | Mean (SD) | | Test of overall trend | | |
|---|---|---|---|---|---|---|---|
| | | N | Baseline | Follow-up | Effect | F | *P* |
| Well-being | | | | | | | |
| Anxiety (STAI-state) | ≤1 year | 11 | 45.5 (12.5) | 49.4 (11.2)* | t.s.d. | 6.02 | 0.02 |
| | >1 year | 12 | 35.8 (8.7) | 40.5 (9.5)* | Time | 3.65 | 0.07 |
| | | | | | Interact | 0.03 | 0.87 |
| Depression (CESD) | ≤1 year | 11 | 11.9 (8.3) | 15.0 (7.7) | t.s.d. | 2.81 | 0.11 |
| | >1 year | 12 | 5.7 (7.5) | 10.7 (9.4) | Time | 8.59 | 0.01 |
| | | | | | Interact | 0.48 | 0.50 |
| Cancer related distress (IES) | ≤1 year | 11 | 22.5 (12.4) | 30.4 (11.7)* | t.s.d. | 5.53 | 0.03 |
| | >1 year | 11 | 12.7 (12.5) | 20.1 (11.2)* | Time | 7.78 | 0.01 |
| | | | | | Interact | 0.01 | 0.92 |
| General health | ≤1 year | 11 | 7.4 (1.4) | 6.8 (1.7) | t.s.d. | 3.29 | 0.09 |
| | >1 year | 11 | 8.3 (0.9) | 7.5 (1.1) | Time | 3.28 | 0.09 |
| | | | | | Interact | 0.13 | 0.72 |

t.s.d., time since diagnosis; Interact, interaction between time since diagnosis and time.
*Significant difference ($P \leq 0.05$) between affected women diagnosed ≤1 year and >1 year at follow-up (independent *t*-test).

assess the differential impact on affected opposed to unaffected women. We found that both groups showed a similar increase on these outcomes, with a hint towards a more profound impact on affected women. We also found that affected women diagnosed ≤1 year previously reported an elevated general and cancer specific distress compared to women diagnosed >1 year both at baseline and at follow-up. With respect to treatment choice, more affected women intended to obtain prophylactic surgery and valued it higher at both time points. With respect to the other decision making outcomes, affected women had a lower preference for decision making at baseline; no differences were found at follow-up. At follow-up, both affected and unaffected women showed an increase in strength of treatment preference and a decrease in decision uncertainty.

## Well-Being

Previous studies evaluating the impact of genetic testing and a positive test result, showed low levels of general and cancer related distress [Lerman et al., 1996; Croyle et al., 1997; Lodder et al., 1999, 2001; Coyne et al., 2000; Wood et al., 2000; Schwartz et al., 2002]. Also in our study, mean levels of anxiety, depression, and cancer related distress were below clinically significant levels. Women who had received a positive test result reported a significant increase in anxiety, depression, and cancer related distress. Although this seems logical, most previous studies showed no increased distress in mutation carriers [Lerman et al., 1996; Croyle et al., 1997; Lodder et al., 2001; Schwartz et al., 2002]. Only one study [Wood et al., 2000] found a non significant

TABLE VI. Treatment Intentions at Baseline and at Follow-Up for Affected and Unaffected Mutation Carriers

| | | | PM | BS | ? | Total |
|---|---|---|---|---|---|---|
| | | | Follow-up intentions breasts | | | |
| Affected | Baseline intentions breasts | PM | 7 | 2 | — | 9 |
| | | BS | 1 | 9 | — | 10 |
| | | ? | 1 | 1 | — | 2 |
| | | Total | 9 | 12 | — | 21 |
| Unaffected | | PM | 12 | 3 | 1 | 16 |
| | | BS | 4 | 37 | 1 | 42 |
| | | ? | 2 | 3 | 1 | 6 |
| | | Total | 18 | 43 | 3 | 64 |
| | | | Follow-up intentions ovaries | | | |
| | | | PO | OS | ? | |
| Affected | Baseline intentions ovaries | PO | 12 | — | — | 12 |
| | | OS | 1 | 2 | — | 3 |
| | | ? | 5 | 1 | — | 6 |
| | | Total | 18 | 3 | — | 21 |
| Unaffected | | PO | 28 | 6 | 1 | 35 |
| | | OS | 8 | 11 | 2 | 21 |
| | | ? | 2 | 1 | 2 | 5 |
| | | Total | 38 | 18 | 5 | 61 |

PM, prophylactic mastectomy; BS, breast cancer screening; PO, prophylactic oophorectomy; OS, ovarian cancer screening; ?, undecided.

trend towards an increase in distress. This study included a small sample size of affected mutation carriers (n = 10). Earlier studies [Lerman et al., 1996; Croyle et al., 1997], with 53 and 25 mutation carriers respectively, did not show an increase in distress. However, they included both men and women who were aware that a *BRCA1/2* mutation was segregating in their family, and who had been participating in genetic studies for a long time. This highly selected sample may not be representative for a clinic-based population. However, two other clinic-based studies also did not find an increase in distress [Lodder et al., 2001; Schwartz et al., 2002]. One study [Lodder et al., 2001] included a small sample of unaffected mutation carriers only (n = 25). The other study [Schwartz et al., 2002] included a larger sample of both affected index cases (n = 43) and their unaffected relatives (n = 35), but their follow-up assessment was 6 months after disclosure of the test result whereas ours was after 2 weeks. Therefore, it is conceivable that either a small sample size or a long interval between test result and assessment, have masked the short-term negative effects on general and cancer related distress in mutation carriers in previous studies. The point in time at which our follow-up questionnaire was filled out may have contributed to our finding of an increase in distress; it is unlikely that psychological reactions are fully balanced and that adaptation is complete so shortly after learning their carrier status. Possibly, a positive test result causes transient distress on the short term only.

### Differential Well-Being in Affected Versus Unaffected Women

Affected women scored higher on depression and cancer related distress and lower on general health at baseline, and tended to score higher on anxiety at follow-up. We assume that having a cancer history and especially a short time since cancer diagnosis explained the increased distress in affected women. Indeed, we found that affected women diagnosed $\leq$1 year previously had higher distress levels as those diagnosed $>$1 year, who scored almost identical as unaffected women. This was also found in a previous study [Wood et al., 2000].

Other confounding variables, such as being an index case (meaning that usually more time is needed for DNA-analysis and facing the task of informing their family after a positive test result) or older age, are also candidates for explaining the worse well-being of affected women at baseline. However, they could be ruled out as explanation because in a previous study [Randall et al., 2001] was found that levels of distress in affected women did not depend on whether or not genetic testing was initiated. We checked whether older age was associated with an increased distress level, but this was not the case (data not shown).

Furthermore, affected women tended to experience a stronger increase in anxiety and cancer related distress after a positive test result when compared to unaffected women; within the group of affected women, this was independent of time since diagnosis. We can only speculate about the cause of this greater emotional reactivity. A plausible explanation might be that affected women are additionally distressed as a consequence of a reactivation of negative feelings related to their previous cancer diagnosis and treatment; they do not only have to cope with their carrier status, but also to re-evaluate their disease in the light of this new information. Other explanations are suggested by previous studies; one indicated that affected index cases experienced difficulties in transmitting their results to families [Bonadona et al., 2002], and another suggested that affected women reported more distress after a positive test result because they had underestimated its impact [Dorval et al., 2000].

### Associations Between Decision Uncertainty and Well-Being

Well-being is expected to be worse in women who feel more uncertain about which treatment to choose. Indeed, after disclosure of a positive test result, we found that a worse well-being was associated with a *higher* decision uncertainty; the correlations of decision uncertainty with anxiety, depression, cancer related distress, and general health were 0.34 ($P = 0.00$), 0.28 ($P = 0.01$), 0.39 ($P = 0.00$), and $-0.30$ ($P = 0.01$), respectively. At baseline, however, when the treatment choice is still hypothetical, no such association were found (data not shown). These findings underline the impact of the decision making process on well-being after a positive test result.

Surprisingly, we found that over time, a worse well-being was concomitant with a *lower* decision uncertainty (see Table III). Several explanations could be given. Possibly, women may be more certain about their treatment choice, simply because they are certain about their carriers status. Another explanation is that mutation carriers who feel more certain about their choice, also have a stronger feeling that they have no choice and therefore experience a loss in well-being. Furthermore, women might bolster their decision to cope with the distress caused by a positive test result; in other words, fear and distress may induce a wish to act firmly.

### Limitations

Several limitations should be considered. First, the sample of mutation carriers is relatively small. Nevertheless, it is the greatest consecutive clinic-based sample of mutation carriers to date to study differences between affected and unaffected women. Because we included a consecutive sample, heterogeneity exists in our sample. Not all affected women were an index case, some were members of a family in which a mutation was found before. And not all unaffected women were part of a family with a known mutation, some were index cases themselves. Second, all of our mutation carriers had received an informative decision aid. Thus, it could be argued that changes in well-being, treatment choice, and decision making outcomes were a result of the informative decision aid and not of disclosure of a positive test result. However, the informative decision

aid did not affect well-being, strength of treatment preference, decision uncertainty, and preference for decision making, although it did lead to more considerations towards prophylactic surgery and higher valuations for prophylactic surgery and lower valuations for screening [Van Roosmalen et al., 2002b]. Therefore, it is reasonable to attribute the impact of a positive test result on well-being, strength of treatment preference, and decision uncertainty, to disclosure of a positive test result and not to the informative decision aid. Third, long term follow-up was not obtained because in the second part of our study, mutation carriers will be randomized to a second decision aid, consisting of value assessment and individualized treatment information derived from a decision model [Van Roosmalen et al., 2002a], or to the control group. The follow-up time point reported here, will be the baseline assessment for this second intervention.

### Clinical Recommendations

In the Netherlands, protocols for psychosocial care in genetic counseling for a possible *BRCA1/2* mutation are often based on previous experience from predictive testing for Huntington disease [Bleiker et al., 2001]. A very important difference with a hereditary breast/ovarian cancer syndrome is that it is not possible to prevent Huntington disease or to detect it in an early curable stage. Furthermore, there exists no sporadic form of the disease; people affected by Huntington disease always carry the mutation. Finally, Huntington disease is always fatal. Consequently, there is no group of affected mutation carriers for whom DNA-diagnosis implicates a substantial change in prognosis or probability to develop a new serious disease. In contrast to this situation, the large majority of breast cancers is sporadic and relatives of sporadic breast cancer patients usually only face a minor increase in breast cancer risk. Diagnosing a *BRCA1/2* mutation in a breast cancer patient implicates a large probability of developing a second primary breast cancer and/or ovarian cancer. Until now, protocols for psychosocial care in genetic counseling for a possible *BRCA1/2* mutation have been mainly tailored towards unaffected women, analogous to the protocol for Huntington disease [Bleiker et al., 2001]. Our results indicate that this may not be justified. Affected women, especially those who have been recently diagnosed with cancer, may need more support than unaffected women. We suggest to follow this group more closely and to stimulate contact with a psychosocial worker for support. Our research does not permit us to give specific recommendations about the form of these interventions but this should be the topic of further research.

## ACKNOWLEDGMENTS

We are grateful to all the women who participated in this study. The authors thank the research assistants Monique Oude Elberink and Ineke Bakker for their excellent work. We acknowledge the support of the participating Family Cancer Clinics.

## REFERENCES

Bleiker EMA, Grosfeld FJM, Hahn DDE, Honing C, on behalf of the Dutch Cancer Society for Psychosocial Oncology Working Group of Familial Cancer. 2001. Psychosocial care in family cancer clinics in the Netherlands: A brief report. Patient Educ Couns 43:205–209.

Bonadona V, Saltel P, Desseigne F, Mignotte H, Saurin JC, Wang Q, Sinilnikova O, Giraud S, Freyer G, Plauchu H, Puisieux A, Lasset C. 2002. Cancer patients who experienced diagnostic testing for cancer susceptibility: Reactions and behavior after disclosure of a positive test result. Cancer Epidemiol Biomarkers Prev 11:97–104.

Coyne JC, Benazon NR, Gaba CG, Calzone K, Weber BL. 2000. Distress and psychiatric morbidity among women at high-risk breast and ovarian cancer familes. J Consult Clin Psychol 68:864–874.

Croyle RT, Smith KR, Botkin JR, Baty B, Nash J. 1997. Psychological responses to BRCA1 mutation testing: Preliminary findings. Health Psychol 16:63–72.

Deber RB, Kraetchmer N, Irvine J. 1996. What role do patients wish to play in treatment decision making. Arch Intern Med 156:1414–1420.

Dorval M, Farkas Patenaude A, Schneider KA, Kieffer SA, DiGianni L, Kalkbrenner KJ, Bromberg JI, Basili LA, Calzone K, Stopfer J, Weber BL, Garber JE. 2000. Anticipated versus actual emotional reactions to disclosure of results of genetic tests for cancer susceptibility: Findings from p53 and BRCA1 testing programs. J Clin Oncol 18:2135–2142.

Easton DF, Ford D, Bishop DT, Breast Cancer Linkage Consortium. 1995. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Am J Hum Genet 56:265–271.

Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponders BAJ, Gayther SA, Birch JM, Lindblom A, Stoppa-Lyonnet D, Bignon Y, Borg A, Hamann U, Haites N, Scott RJ, Maugard CM, Vasen H, Seitz S, Cannon-Albright LA, Schofield A, Zelada-Hedman M, Breast Cancer Linkage Consortium. 1998. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 62:676–698.

Horowitz M, Wilner N, Alvarez W. 1979. Impact of event scale: A measure of subjective stress. Psychosom Med 41:209–218.

Lerman C, Narod S, Schulman K, Hughes C, Gomez-Caminero A, Bonney G, Gold K, Trock B, Main D, Lynch J, Fulmore C, Snyder C, Lemon SJ, Conway T, Tonin P, Lenoir G, Lynch H. 1996. BRCA1 testing in families with hereditary breast-ovarian cancer: A prospective study of patient decision making and outcomes. JAMA 275:1885–1892.

Lodder LN, Frets PG, Trijsbrug RW, Meijers-Heijboer EJ, Klijn JGM, Duivenvoorden HJ, Tibben A, Wagner A, Van der Meer CA, Devilee P, Cornelisse CJ, Niermeijer MF, and other members of the Rotterdam/Leiden Genetics Working Group. 1999. Presymptomatic testing for BRCA1 and BRCA2: How distressing are the pre-test weeks? J Med Genet 36:906–913.

Lodder L, Frest PG, Trijsburg RW, Meijers-Heijboer EJ, Klijn JGM, Duivenvoorden HJ, Tibben A, Wagner A, Van der Meer CA, Van den Ouweland AMW, Niermeijer MF. 2001. Psychological impact of receiving a BRCA1/BRCA2 test result. Am J Med Gen 98:15–24.

Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katcher H, Yakumo K, Gholami Z, Shaffer D, Stone S, Bayer S, Wray C, Bogden R, Dayananth P, Ward J, Tonin P, Narod S, Bristow PK, Norris FH, Helvering L, Morrison P, Rosteck P, Lai M, Barret JC, Lewis C, Neuhausen S, Cannon-Albright L, Goldgar D, Wiseman R, Kamb A, Skolnick MH. 1994. A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. Science 266:66–71.

O'Connor AM. 1995. Validation of decision conflict scale. Med Decis Making 15:25–30.

Radloff LS. 1977. The CES-D scale: A self-report depression scale for research in general population. Appl Psychol Meas 1:385–401.

Randall J, Butow P, Kirk J, Tucker K. 2001. Psychological impact of genetic counselling and testing in women previously diagnosed with breast cancer. Intern Med 31:397–405.

Schwartz MD, Peshkin BN, Hughes C, Main D, Isaacs C, Lerman C. 2002. Impact of BRCA1/BRCA2 mutation testing on psychologic distress in a clinic-based sample. J Clin Oncol 20:514–520.

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. 1983. Manual for the State-Trait Anxiety Inventory (Form Y). New York: Consulting Psychologists Press, Inc.

Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. 1997. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 336:1401–1408.

Van Roosmalen MS, Verhoef LCG, Stalmeier PFM, Hoekstra-Weebers JEHM, Oosterwijk JC, Hoogerbrugge N, Moog U, Van Daal WAJ. 2002a. A decision analysis of prophylactic surgery or screening for BRCA1 mutation carriers: A more prominent role for prophylactic oophorectomy. J Clin Oncol 20:2092–2100.

Van Roosmalen MS, Stalmeier PFM, Verhoef LCG, Hoekstra-Weebers JEHM, Oosterwijk JC, Hoogerbrugge N, Moog U, Van Daal WAJ. 2002b. Randomized trial of a decision aid and its timing for women being tested for a BRCA1/2 mutation. (Submitted).

Whittemore AS, Gong G, Itnyre J. 1997. Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: Results from three U.S. population-based case-control studies of ovarian cancer. Am J Hum Genet 60:496–504.

Wood ME, Mullineaux L, Kulchak Rahm A, Fairclough D, Wenzel L. 2000. Impact of genetic testing on women with cancer: A pilot study. Genet Test 4:265–272.

Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G, Barfoot R, Hamoudi R, Patel S, Rice C, Biggs P, Hashim Y, Smith A, Connor F, Arason A, Gudmundsson J, Ficenec D, Kelsell D, Ford D, Tonin P, Bishop DT, Spurr NK, Ponder BAJ, Eeles R, Peto J, Devilee P, Cornelisse C, Lynch H, Narod S, Lenoir G, Egilsson V, Barkadottir RB, Easton DF, Bentley DR, Futreal PA, Ashworth A, Stratton MR. 1995. Identification of the breast cancer susceptibility gene *BRCA2*. Nature 378:789–1992.